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OPTICAL COUPLING DEVICE AND METHOD

The present invention relates to a device and a method for optically coupling a first optical element to a second optical element.

It is known in the field of optical metrology to insert means for index adaptation between separate optical elements such as, for example, a beam guiding member, on the one hand, and a sample carrier, on the other hand, such that the transition of optical radiation from one optical element to the other can occur with the least possible loss. The term "index adaptation" means here the adaptation of the refractive index.

An example of a measurement system in which such index-adapting means are used are SPR measurements. SPR stands for "Surface Plasmon Resonance".

SPR technology is an established method for marker-free detection of receptor-ligand interaction. This will be briefly explained with reference to Fig. 1A. In SPR, a glass substrate 1 is usually coated with a thin gold film 2, and one of the binding partners 3 is chemically immobilized on this gold surface (e.g., proteins are immobilized using a gel, or small molecules are immobilized on the surface by means of self-assembled monolayers (SAM)). The second binding partner 4, dissolved in the liquid 5, i.e. as sample liquid, is brought into wetting contact with the chemically modified gold surface. If the dissolved partner binds to the partner immobilized on the surface, the refractive index in the liquid layer right above the gold surface changes.

This refractive index change can be detected by means of
plasmon resonance: Light is shone in through the glass
substrate and is reflected at the gold layer. Under specific
physical boundary conditions (angle of reflection, angle of
polarization and radiation wavelength, refractive index of
substrate and liquid, thickness of the gold layer), the light
is not, however, reflected but absorbed. It is then that
plasmon resonance occurs, i.e. the light energy is converted
to an electron charge density wave along the gold/liquid
interface. In practice, one of the two physical parameters of
the light, i.e. angle of incidence (Fig. 1B) or wavelength
(Fig. 1C), is now tuned and the intensity of the reflected
light is detected as a function of this parameter. By this
means, a reflection spectrum is obtained in which a drop in
intensity (so-called SPR dip, see Figs. 1B and 1C) can be
observed once the resonance condition is reached. The minimum
of this intensity drop is displaced once the refractive index
of the liquid layer above the gold changes owing to the
bonding of the reaction partner. It can be proven (for
example, by way of experiment) that this displacement of the
minimum ($\Delta\vartheta$ or $\Delta\lambda$) is directly proportional to the surface
density of the bound molecules.

To technically implement this measuring process, use is
commonly made of the so-called *Kretschmann* geometry (Fig.
1A). The reflection angle at which resonance occurs (the
reflection angle for SPR with gold on glass and aqueous
solutions is approx. 65-70°C) lies, however, above the total
reflection angle for the glass/air interface, i.e. in the
case of a substrate in the form of a thin glass plate 11, the
light cannot be shone in from the underside of the glass
since no angle of incidence exists which after refraction of
the light would result in an angle suitable for SPR.
Furthermore, light which is reflected at the gold layer at an
SPR angle does not leave the substrate but is rather directed

within the substrate by means of multiple total reflection
and can therefore no longer be detected in a spatially
resolved manner (see Fig. 2A). Therefore, a prism 12 is used
in the *Kretschmann* system which allows the light to penetrate
into its side window at a small or entirely negligible angle
of incidence and to then be reflected at the gold layer 2 at
the angle large enough for SPR before exiting again from the
other side window (see Fig. 2B).

Since it is disadvantageous economically to employ a new
prism for each experiment, thin glass substrates 11 are
normally used which carry the gold sensor surface 2 and are
placed on top of a prism that can always be reused, with the
gap between prism and glass substrate being filled with an
index-adapting layer 13 (see Fig. 2C).

The index-adapting layer can be implemented in several
possible ways, i.e. as
-       a liquid index oil which runs into a thin capillary gap,
or
-       a thin layer of resilient silicone material (index
matching rubber) as described, for example, in WO 97/19375.

Both methods have disadvantages associated therewith, in
particular as regards large-surface sensor plates:

In the case of the oil method, the only possibility of
removing the oil from the capillary gap is to open the
capillary gap and to carry out a manual cleaning process.
Also, air bubbles sometimes materialize when the capillary
gap is being filled. The capillary gap must moreover be
opened again to remove these bubbles.

The method with the index rubber presents a problem in the
case of flat substrates since air bubbles tend to be trapped

therein even if the rubber has a structure which expels the
air in a defined manner when being pressed against. Total
reflection occurs at the locations of the bubbles, and the
location beneath on the sensor surface is then not visible.

If a bubble materializes in the rubber layer, it must be
assumed that this has something to do with unevenness (the
rubber mat does not fit at all points exactly between glass
plate and prism). Thus, a new rubber mat must be used, on the
flatness/homogeneity of which high demands are placed. This
is very disadvantageous.

The problems described above are not limited to SPR
measurement systems, they rather occur in general when the
attempt is made to adapt the index between two optical
elements. It should be noted that for purposes of the present
description and the present claims, the term "optical" refers
to any radiation capable of being passed through appropriate
elements, i.e. is not limited to the visible range of the
electromagnetic spectrum.

The object of the present invention is to provide an improved
device and an improved method for optically coupling two
separate elements.

This object is solved by a device having the features of
claim 1 and a method having the features of claim 13.
Preferred embodiments are described in the dependent claims.

According to the present invention, an index-adapting liquid
is used as an index-adapting means, however, no capillary gap
is employed. The present invention rather provides the
formation of a chamber formed by radiation penetration
surfaces of a first and a second optical element to be
coupled, and is delimited by a circumferentially closed side

wall which connects the two radiation penetration surfaces.
Also provided is a feeding conduit for supplying index-
adapting liquid into the chamber, as well as a discharge
conduit for evacuating index-adapting liquid from the
chamber. Thus, the chamber represents some sort of flow cell
for the index-adapting liquid (e.g. index oil), with the
liquid transportation being determined, at least not to a
dominant extent, by capillary forces. It is possible by this
means to easily and reliably achieve an optical coupling
between the first and the second optical element by filling
index-adapting liquid into the chamber via the feeding
conduit. It is possible thereby to avoid, on the one hand,
the problems arising with capillary gaps, since the chamber
is dimensioned such that the index-adapting liquid can easily
flow between the feeding conduit and the discharge conduit,
and, on the other hand, the problems associated with index-
adapting rubbers, since it is not a solid that is selected as
the index-adapting means. The present invention offers in
particular the advantage of being easily automatable as the
index-adapting liquid can be supplied into and evacuated from
the chamber by means of an automatic control system.

According to a preferred embodiment, a tilting means is
provided so that the entire system can be brought into a
tilted position in which the point at which index-adapting
liquid is supplied into the chamber is disposed at a lower
level, as viewed in the direction of gravity, than a point of
discharge and/or air escape. By this means, bubble-free
filling of the chamber is particularly simple since the air
or gas bubbles rise upward and are expelled through the air
escape point situated farther above by the index-adapting
liquid supplied from below, whereas no bubbles are left in
the index-adapting liquid.

The present invention will now be described in more detail
with reference to the accompanying drawings in which:

Fig. 1   is a schematic diagram showing a prism and a sensor
            as well as measuring curves explaining the
            principle of surface plasmon resonance;

Fig. 2   shows schematic elements for SPR measurements;

Fig. 3A   shows individual elements of a device according to
            a first embodiment of the invention;

Fig. 3B   shows the composed elements of Fig. 3A and explains
            the operation according to a preferred embodiment;

Fig. 4A   shows elements of an array for supplying sample
            liquid onto a sensor area of the second optical
            element;

Fig. 4B   shows the composed elements of Fig. 4A explaining a
            preferred operating method;

Fig. 5   shows a complete measurement set-up with several
            sample vessels;

Fig. 6   is a schematic view of the radiation path for
            feeding radiation to the first and second optical
            elements or for removing it therefrom; and

Fig. 7   shows a further embodiment of the device according
            to the invention.

Detailed examples will now be described. Fig. 3A shows
elements of a device according to the invention. Reference
number 12 refers to a first optical element shown as a prism.

Reference number 30 refers to a second optical element shown
as a platelet. The first optical element 12 has a first
radiation penetration surface 121, and the second optical
element 30 has an opposite second radiation penetration
surface 32. Optical coupling is to take place between the
first and second optical elements via the respective
radiation penetration surfaces.

An intermediate element 20 having a space 25 is provided
between the first optical element 12 and the second optical
element 30. Said space 25 defines a side wall 21 in the
intermediate piece 20. Furthermore, channels 15 are provided
in the first optical element 12 through which index-adapting
liquid or gas may flow.

According to this embodiment, the intermediate piece 20 and
the second optical element 30 are placed on the first optical
element 12 in such a manner that the space 25 forms a chamber
in which the channels 15a, 15b respectively form a feeding or
discharge conduit. The circumferentially closed side wall 21,
a first section of the first radiation penetration surface
121, formed by projection of the side wall 21 on the first
radiation penetration surface 121, and a second section of
the second radiation penetration surface 32, formed by
projection of the circumferentially closed sidewall 21 on the
second radiation penetration surface 32, form a chamber which
is closed except for the feeding and discharge conduits. The
expression "circumferentially closed" means in this regard
that the projection of the side wall defines a closed
circumferential line.

Index-adapting liquid can be filled into this chamber for the
purpose of adapting the index between the first optical
element 12 and the second optical element 30. Supply and
discharge can thereby occur through one channel, the other

channel then being used purely for the purpose of air escape,
or one channel can be used for supply and the other for
discharge of the index-adapting liquid so as to form some
sort of flow cell.

The channels 15a, 15b shown in the Figure can be produced in
the first optical element 12 in any suitable manner, for
example by ultrasound machining, sawing or milling or also by
using photolithographic means. Although the channels 15a, 15b
are preferably formed in the first optical element 12, as
shown in Fig. 3A, they can also be formed individually or
jointly in the intermediate element 20 or the second optical
element 30. Thus, one or both of the channels might be
formed in the intermediate element 20 and might enter the
chamber through the side wall 21.

The intermediate element 20 can be made of any suitable
material such as, for example, glass. The space 25 of the
intermediate element 20 preferably has the cross-sectional
shape shown in Fig. 3A, namely a rectangular center portion
and two triangular end portions which cooperate with the
channels such that the tips of the triangular end portions
respectively face the feeding conduit 15a or the discharge
conduit 15b (see also Fig. 3B). In other words, the cross-
section of the space 25 preferably has a double-trapezoid
shape.

The space can be produced by any suitable method, for example
by laser machining or punching, depending on the material
selected for the intermediate element 20. The V-shaped tips
of the double trapezoid lie as exactly as possible on the
ends of the channels 15a, 15b, such that there the index-
adapting liquid (e.g. index oil) can flow through the
respective channel and into or out of the chamber between the
first optical element 12 and the second optical element 30.

The thickness of the intermediate element 20 is such that the
capillary action of the delimiting surfaces (the first
section in the first radiation penetration surface, the
second section in the second radiation penetration surface
and the side wall 21) is so low that the index-adapting
liquid can flow without major resistance and/or that the
liquid transportation is not determined to a dominant extent
by capillary forces.

The intermediate element 20 is preferably adhered onto the
first optical element 12 so as to form a permanent unit from
the first optical element and the intermediate element 20
since in this manner the tips of the double trapezoid need to
be adjusted only once in relation to the two channels 15a,
15b.

The second optical element 30, which is preferably a platelet
carrying a measurement sample to be analyzed using radiation,
is preferably detachably placed on the intermediate element
20. This can be done, for example, by means of an assembly
including spring clips.

Fig. 7 shows an alternative to the embodiment in Fig. 3a.
Fig. 7 shows, in turn, a first optical element 12 (e.g. a
prism) with a first radiation penetration surface 121, as
well as a second optical element 30 (e.g. a platelet with a
sensor area or measurement sample 31) having a second
radiation penetration surface 32 which is opposite to the
first radiation penetration surface 121.

In the example of Fig. 7, the first optical element 12 has a
groove 26. The groove has a side wall 21, with the bottom of
the groove 26 and the side wall 21 forming, together with the
remaining surface of the first optical element 12 facing the
second optical element 30, the (complete) radiation

penetration surface 121. In other words, the bottom of the
groove 26 is part of the radiation penetration surface 121,
the radiation penetration surface 121 being thus disposed,
however, in two different planes.

The channels 15a, 15b lead into the groove 26, and therefore,
if the second optical element 30 is placed (preferably
detachably) on the first optical element 12, a chamber is
defined by the groove 26, said chamber being closed except
for the channels 15a, 15b so as to hold index-adapting liquid
and to thus optically couple the first to the second optical
element. In other words, the section in the surface of the
first optical element 12 which is defined by the side wall 21
is smaller than the complete surface, as can be seen in
Figure 7, however, the second section which is defined by
projection of the side wall 21 on the second optical element
30 is also smaller than the surface area of the second
radiation penetration surface 32 on the second optical
element 30.

The materials and manufacturing techniques to be used in the
example of Fig. 7 are the same as those in the example of
Fig. 3A. It should be noted that the configurations of Figs.
3A and 7 can also be combined, i.e. a chamber can be formed
both by a groove 26 and a space 25 in an intermediate element
20 such that the chamber is formed in each case in part by
the groove and in part by the space.

In Figure 7, the cross-sectional shape of the groove 26 is
illustrated as being oval. The cross-section could also have
the double-trapezoid shape of the space 25 of the
intermediate element 20 in Fig. 3A; it is possible just as
well for the space 25 in Fig. 3A to have the oval shape of
the groove 26 in Fig. 7. In principle, the cross-section of
the space 25 or the groove 26 can be selected to have any

suitable shape, the double-trapezoid shape shown in Fig. 3A
being, however, preferred since it ensures an improved supply
and discharge of index-adapting liquid.

As already mentioned, the second optical element 30 is
preferably mounted so as to be detachable. It should be noted
that this will normally result in a small gap between the
second optical element 30 and the surface 121 (in the example
of Fig. 7) or the intermediate element 20 (in the example of
Fig. 3A), with the capillary forces in this small gap
preventing, however, the index-adapting liquid from passing
through, thus forming nonetheless a chamber which is closed
at least for the index-adapting liquid.

Fig. 3B shows an arrangement in which the individual elements
shown in Fig. 3A are joined, and additionally shows a supply
means 41, 42, 43 for supplying index-adapting liquid, as well
as elements 45, 46 which represent a tilting means with which
the complete array can be tilted at an angle α such that the
point of supply of index-adapting liquid is disposed, as
viewed in the direction of gravity, at a level lower than the
point of discharge. The supply device can be formed, for
example, by a reciprocable syringe 42, a tube 41 and one or
two cannulae 43, said cannulae 43 being inserted in the
channels 15a, 15b (see Fig. 3A).

The elements 45 and 46 are illustrated only schematically,
with 45 being a stop and 46 an element for lifting the first
optical element 12, for example by means of an electric motor
(not shown). The tilting of the array at an angle α ensures
that a horizontal liquid front 40 is formed as a result of
gravity and that the air (or the gas present in the chamber)
can escape in a defined manner through the channel 15b
situated farther above.

The index-adapting liquid can be removed again upon
termination of measurements either by being drawn back into
the syringe 42 or by air being pressed through the chamber,
thus expelling the index-adapting liquid from the outlet
channel 15b. The entire filling and emptying process with
index-adapting liquid can be easily automated using motorized
syringe drives.

As already mentioned previously, the second optical element
30 is preferably a carrier comprising one or more sensor
fields 31. Although the Figures, to provide greater clarity,
show only one sensor field 31, the second optical element 30
can, of course, also carry more such fields. These fields can
be, for example, SPR sensor fields, i.e. sensor fields
provided on the side of the optical element 30 facing away
from the second radiation penetration surface 32. A thin
layer suitable for SPR (e.g. gold) is applied to this side
facing away, on which, in turn, specific ligands are
immobilized. Measurement occurs by illuminating the sensor
fields from the body of the platelet 30.

The arrangement of the one or more sensor fields 31, the
dimensions of the groove 26 or space 25 and the supply of
radiation to the first optical element are preferably such
that the entire surface of the one or more sensor fields 31
is illuminated from the body of the second optical element 30
and that the light reflected from this area can completely
exit the prism. In other words, the space 25 should be
dimensioned to be so large that it does not act as a screen
with regard to the sensor field 31.

It should be noted that the supply means 41, 42, 43 and the
tilting means 45, 46 can also be used in the configuration
of Figure 7 in order to achieve the same effects. It is
possible by means of the arrangements described above to

achieve a defined, bubble-free and conveniently automatable
filling of index-adapting liquid into a chamber connecting
the first and second optical elements. This presents an
advantage especially in connection with the use of sensor
plates as the second optical element that are detachably
mounted on the array, since index-adapting liquid can be
conveniently filled into the chamber after mounting of the
sensor plate and can be removed therefrom again after
measurement, whereupon the sensor plate can be removed and a
new measurement can be started, for example by mounting
another sensor plate.

In case that a sensor plate, for example an SPR sensor plate
having sensor fields on the side facing away from the second
radiation penetration surface 32, is used as the second
optical element, additional elements are preferably provided,
as shown in Figs. 4A and 4B. A thermostatable block 50 with
a first fluid-conducting channel 55 and a second fluid-
conducting channel 56, as well as a gasket 52 are disposed on
the side of the plate 30 having one or more sensor fields 31.
The gasket 52 surrounds the one or more sensor fields 31 and
thus cooperates with the thermostatable block 50 such that a
space is formed around the one or more sensor fields in which
sample liquid intended for interaction with the one or more
sensor fields 31 can be fed or discharged through the first
fluid-conducting channel 55 and/or the second fluid-
conducting channel 56. The formed space thereby presents
some kind of flow cell for sample liquid.

As shown in Fig. 4B, the use of this system is particularly
preferred in combination with the already described tilting
means since the point of supply of sample liquid can then be
set lower, as viewed in the direction of gravity, than the
point of discharge and/or air escape so as to permit bubble-
free supply of sample liquid.

The thermostatable block 50 can be, for example, a metal
block with an inert coating 51. Thermostatting of the metal
block can take place by means of either a Peltier element or
additional bores in the metal block and a circulation
thermostat. The gasket 52, which has preferably the cross-
section of a double-trapezoid, borders the one or more sensor
fields 31 on the plate 30. The metal block has bores 55 and
56 as fluid-conducting channels. These bores are designed to
match the V-shaped corners above the gasket 52. The coating
51 can be implemented in any suitable manner, for example
using PTFE, or it can be realized as a thin glass platelet
which is adhered onto the metal block and likewise has
through-holes at the locations of the bores 55 and 56.

The thickness of the gasket 52 defines the layer thickness of
the resulting space which is delimited at the top by the
metal block and at the bottom by the sensor plate 30. Sample
liquid is introduced into the bore 55 via a sheathed line 57
and a syringe 59. As already described, the angle of
inclination/tilt angle α ensures that a horizontal liquid
front 58 is formed in the flow cell so as to prevent bubble
formation. The expelled air escapes from the outlet 56,
which is thus designed as an air escape connection. The
gasket is preferably dimensioned such that no substantial
capillary forces arise in order that the flow of sample
liquid into the resulting space is not impeded to a
substantial extent, thus enabling quick liquid
transportation.

The space can be emptied by the liquid being drawn back into
the syringe 59 or by air being pressed through the supply
channel 55 in order to expel the sample liquid from the
second conducting channel 56. It is also possible to expel a
specific sample liquid by supplying another sample liquid or
a specific rinsing liquid (e.g. pure water).

The combination of the arrays according to Fig. 3 or 7 with
the array according to Fig. 4 permits a particularly
preferred implementation of a measuring apparatus, in
particular an SPR measuring apparatus. For this, it is
possible to move both the index-adapting liquid and the
various sample liquids using automated syringe drives.

A schematic view of a complete measurement array is shown in
illustration 5. The array is adapted to allow several
different sample liquids to be sequentially washed over the
one or more sensor fields 31. For example, this may be first
a reference buffer, then a sample liquid, then again a
reference buffer, a sample liquid, etc., with one measurement
being carried out for each liquid by recording a spectrum
(e.g. an SPR spectrum) to characterize the interactions
between the respective sample liquid and the one or more
sensor fields.

In the schematic measurement array of Fig. 5, syringe drives
with a three-way valve 64 (also called diluter) and a
multivalve 62 are used for the purpose of automation.
Furthermore, a container with system liquid 65, a tube
reservoir 62 and sample vessels 61 are provided. At the start
of measurement, system liquid is initially filled, by
switching over the three-way valve 64 or the multivalve 62,
into the tube reservoir 63 and the tubes to the samples 61
via the three-way valve 64. Thereafter, the tubes are hung in
the sample vessels 61. The first sample liquid can now be
drawn up into the tube reservoir and can then be introduced
into the space formed above the one or more sensor fields 31.
Following measurement, the liquid can be withdrawn from the
space and the second sample liquid can be introduced so as to
enable the second measurement. Alternatively, the first
liquid can also be displaced from the outlet by supplying the
second sample liquid.

Filling of the chamber for index-adapting liquid occurs by means of a further syringe pump 66.

As already mentioned previously, the device according to the invention is preferably used for SPR measurements. The optical assembly for such measurements will now be shown with reference to Fig. 6.

Fig. 6 shows an optical assembly which makes it possible to detect a refractive index change in a liquid layer above the gold surface - caused, for example, by the attachment of one partner in solution to the other partner immobilized on the surface – using the means described above consisting of thermostating block, sensor plate and prism. The assembly corresponds for the most part to the arrangement described in WO 01/63256 A1.

The assembly has the purpose of measuring the wavelength-dependent surface plasmon resonance in the form of reflection spectra.

For this, the white light from a lamp 70 is collimated using an optical system 71 and is coupled into the monochromator 73 using an optical system 72.

The light exiting the monochromator in a cone is transformed via the optical systems 74 and 75 into a light bundle having a cross-section large enough to completely light the active field 31 on the plate 30.

After passing through a polarizer 76, the light is polarized, i.e. the field vector of the light oscillates parallel to the plane of incidence, which is a prerequisite for observing SPR. Optical fibers or fold mirrors can also be used in the illumination ray path described so far, e.g. between 71 and

72 or between 73 and 74, in order to simplify a convenient
structure of the measurement means.

The collimated light passes through the left side of the
prism 12, is then reflected from the gold layer of the sensor
and then exits through the right side 12 of the prism. The
sensor surface is imaged on a CCD detector 78 (or e.g. an
InGaAs detector) through an optical system 77. Since imaging
of the sensor surface is to take place at the angle θ_{spr}, the
detector surface should preferably not be oriented
perpendicularly to the optical axis but rather inclined
thereto. In order to obtain a clearly focused image of the
entire sensor surface, the angle of inclination should meet
the Scheimpflug condition.

The general aspects regarding surface plasmon resonance have
already been described in the introduction and do not,
therefore, have to be repeated here.

Although the present invention has been described with
reference to surface plasmon resonance as the preferred
application, the invention is not limited thereto. It can
rather be used for optically coupling any optical elements.
Even in those cases where it is to be used for coupling
sensor plates as the second optical element, its application
is not limited to surface plasmon resonance but it can rather
be employed in any measuring principle in which the
illumination of samples and/or sensor surfaces on the second
optical element is of interest.